



Original Research Paper

Mechanistic Assessment of Polyendocrine Metabolic Ovarian Syndrome by Plant Derived Multi-Target Therapeutics in Experimental Rat Models

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Key Words	Abstract
DHEA, Esteradiol valerate, letrozole, insulin resistance, Hyperandrogenism	Polycystic Ovary Syndrome (PCOS) is a common endocrine and metabolic disorder affecting women of reproductive age that is marked by hyperandrogenism, ovulatory failure, and polycystic ovarian morphology. PCOS is associated with insulin resistance, obesity, type 2 diabetes, dyslipidaemia, and cardiovascular risk, as well as reproductive issues, making it a significant long-term health concern. Animal models, particularly rat models, have been critical in understanding the pathophysiology of PCOS and evaluating therapeutic options. Letrozole, dehydroepiandrosterone (DHEA), testosterone propionate, and oestradiol valerate are popular induction agents. High-fat or high-sucrose diets exacerbate metabolic symptoms, which are similar to those of PCOS in humans. Medicinal plants have sparked tremendous attention as potential alternatives for synthetic medications due to their antioxidant, anti-inflammatory, insulin-sensitizing, and hormone-regulating properties. Flavonoids, alkaloids, terpenoids, and saponins are some of the phytochemicals that enable these benefits. Research using rat models shows that herbs like <i>Trigonella foenum-graecum</i> (fenugreek), <i>Cinnamomum verum</i> (cinnamon), <i>Curcuma longa</i> (turmeric), <i>Withania somnifera</i> (ashwagandha), and others can help restore the shape of the ovaries, make oestrous cycles more regular, and make the body more sensitive to insulin. Nonetheless, translational value is limited by protocol variability, interspecies differences, and the lack of long-term consequences. This work focusses on contemporary PCOS induction models, evaluates medicinal plant-based therapy in rat models, and tackles translational gaps. <i>Aerva lanata</i> , which is high in polyphenols and has antioxidant and hypoglycemic characteristics, presents a promising but understudied option. To link preclinical findings to clinical application, we must standardise phytotherapy, conduct rigorous randomised trials, and merge humanised and organoid systems.

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Introduction

Overview of Polycystic Ovarian Syndrome (PCOS)

Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine and metabolic condition affecting women of reproductive age. It is defined by hyperandrogenism, ovulatory failure, and polycystic ovarian morphology. Beyond reproductive health, PCOS is linked to metabolic issues such as insulin resistance, obesity, type 2 diabetes, dyslipidaemia, and cardiovascular disease. The heterogeneity of PCOS makes it a complicated condition with a multivariate aetiology that includes genetic, environmental, and behavioural variables.

Prevalence and clinical significance

The global prevalence of PCOS ranges from 6% to 20%, based on diagnostic criteria such as the Rotterdam, NIH, or AE-PCOS Society recommendations Kiran, Z. (2024). The prevalence in India has been found to range between 9% and 36%, depending on area and diagnosis Talukdar et al., 2025. PCOS is not only a leading cause of infertility, but it is also a long-term health problem because it is linked to metabolic syndrome, endometrial cancer, psychological disorders like anxiety and depression, and a lower quality of life (Dhanka et al., 2025; Maulenkul et al.,2024.) As a result, research into effective treatment techniques for PCOS remains a top focus.

Pathophysiology of PCOS

The pathogenesis of PCOS is complex, involving abnormalities in the hypothalamic-pituitary-ovarian (HPO) axis, hyperinsulinemia, and androgen excess. Hypersecretion of luteinizing hormone (LH) and decreased follicle-stimulating hormone (FSH) cause aberrant folliculogenesis and anovulation (Stener-Victorin et al., 2024; Ke et al.,2025). Insulin resistance, which occurs in 50-70% of women with PCOS, exacerbates hyperandrogenism by activating ovarian theca cells to create extra androgens (Unfer et al.,2025). Oxidative stress, chronic low-grade inflammation, and adipokine changes all play important roles in disease progression (Cazzola et al.,2024).

Animal Models in PCOS Research (The Value of Rat Models)

Animal models are critical for understanding the aetiology and pathophysiology of PCOS, as well as testing prospective treatment approaches. Rats are commonly employed as models because of their genetic similarities, consistent oestrous cycle, and ease of hormonal or pharmacological development of PCOS-like symptoms (Li et al.,2025). Letrozole, dehydroepiandrosterone (DHEA), oestradiol valerate, and a high-fat diet are common induction methods that mirror human PCOS symptoms such as hyperandrogenism, cystic ovarian morphology, and metabolic abnormalities Chang et al.,2024. Rat models thus provide a great platform for investigating pharmacological and natural treatments for PCOS.

The role of medicinal plants in PCOS management

In recent years, medicinal plants have received a lot of interest as an alternative and supplemental treatment for PCOS. Many plants include bioactive chemicals, including flavonoids, alkaloids, terpenoids, saponins, and polyphenols, which have antioxidant, anti-inflammatory, insulin-sensitizing, and hormone-regulating activities Al (Raish et al.,2025; Ayyadurai et al.,2026; Sandhiya et al.,2026; Sakthivel et al.,2026; Jancyhelan et al.,2026). Unlike synthetic medications, herbal therapies are regarded as safer, more inexpensive, and culturally acceptable. Several studies in rat models have shown that plants such as *Trigonella foenum-graecum* (fenugreek), *Cinnamomum verum* (cinnamon), *Curcuma longa* (turmeric), and *Withania somnifera* (ashwagandha) can restore ovarian morphology, normalise oestrous cycles, improve insulin sensitivity, and reduce oxidative stress (Dutta et al.,2024; Madamsetty, 2025). Table1 & Figure 1. Thus, medicinal plants are a promising field of research for generating novel and holistic treatments for PCOS

Methodology for Review

Search Strategy

A thorough literature search was carried out to find relevant publications on polycystic ovarian syndrome (PCOS), induction methods, and therapy with medicinal plants in rat models. The electronic databases PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar were searched

between January 2000 and July 2025. The following keywords and Boolean operators were combined: *"Polycystic ovary syndrome" OR "PCOS" AND "rat model" OR "animal model" AND "medicinal plants" OR "herbal treatment" OR "phytotherapy" AND "induction" OR "letrozole" OR "oestradiol valerate" OR "DHEA". A manual search of the collected papers' reference lists was also carried out to discover more relevant studies.

PCOS Induction in Rat Models.

Polycystic ovarian syndrome (PCOS) is a multifactorial endocrine illness whose complicated pathophysiology remains difficult to reproduce in animal models. Rat models are among the most commonly used due to their well-studied reproductive physiology, low cost, and ease of manipulation. Several techniques have been utilised to create PCOS-like phenotypes in rats, roughly classified as hormonal induction, chemical induction, and diet-induced models. Each technique has specific strengths and weaknesses, and the model used is heavily influenced by the research issue being investigated.

Common Methods of PCOS Induction

Hormonal Induction

Letrozole (an aromatase inhibitor).

Letrozole is now the most commonly utilised pharmacological drug to induce PCOS in rat models. The typical strategy for young or adult female rats is to provide 1 mg/kg/day orally for around 21 days. This regimen reduces aromatase activity, reducing oestradiol production and increasing luteinizing hormone (LH) levels, which boosts ovarian androgen synthesis (Wydra et al., 2025; Li et al., 2021). Letrozole-induced rats show persistent diestrus, anovulation, and polycystic ovarian morphology, which includes enlarged cystic follicles and decreased corpora lutea. Combining letrozole with a high-fat diet (HFD) increases metabolic abnormalities such as glucose intolerance, dyslipidaemia, and insulin resistance (Pieczyńska et al., 2022; Zheng et al., 2021). Thus, this paradigm is strongly aligned with the hyperandrogenic phenotype of PCOS.

DHEA (Dehydroepiandrosterone).

Another often utilised drug is DHEA, which is delivered subcutaneously to rats in their prepubertal or peripubertal stages for 20-21 days. DHEA-treated rats exhibit hyperandrogenism, irregular oestrous cycles, cystic ovarian morphology, and persistent anovulation (Mahmoud et al., 2022; Negi et al., 2025). Furthermore, this model frequently reproduces low-grade systemic inflammation and oxidative stress, which are similar to traits seen in women with PCOS. When combined with a high-fat diet, DHEA medication can cause insulin resistance, obesity, and dyslipidaemia (Tovar et al., 2023). Importantly, outcomes differ depending on the age of induction, emphasising the role of developmental timing in PCOS aetiology.

Testosterone

Exogenous androgens, such as testosterone propionate (TP), are frequently used to elicit PCOS-like characteristics. This model is especially effective for investigating androgen excess and its developmental programming consequences. In neonatal or juvenile rats, administering TP (10 mg/kg for 35 days) causes cycle arrest, follicular cysts, and high circulating testosterone levels (Basak et al., 2023; Liu et al., 2025). When paired with high-fat diet, the TP model replicates obesity, dyslipidaemia, and glucose intolerance, enhancing its resemblance to the metabolic phenotype of PCOS (Guo et al., 2022).

Esteradiol valerate (EV).

EV is commonly given as a single intramuscular injection of 2-4 mg to induce persistent oestrus, anovulation, and cystic ovarian morphology (Asghari, et al., 2021). This model is beneficial for researching neuroendocrine regulation of PCOS, as it disrupts ovarian sympathetic innervation (Benitez, et al., 2021). However, unless paired with dietary changes, EV models rarely cause major metabolic abnormalities.

Table 1. List of medicinal plants, their families, types of extracts, common names, and references used in PCOS experimental studies

Botanical name	Family	Extract	Common name	Reference
<i>Crateva religiosa</i>	Capparaceae	Hydroalcohol Lic	Sacred Garlic Pear	Meenaloshini et al.,

<i>G.Forst</i>		Extract		2025
<i>Terminalia chebula</i> Retz	Combretaceae	Ethanollic Fruit Extract	Kadukkai	Kalimuthu et al., 2025
<i>Caesalpinia bonduc</i> (L.) Roxb.	Fabaceae	Aqueous Seed Extracts	Grey nicker,	Ayyadurai et al., 2022
<i>Cyperus esculentus</i> L	Cyperaceae	Tubbers Extract	Tiger nut,	Adelakun S.A. et al., 2022
<i>Calendula officinalis</i> L	Asteraceae	Hydroalcohol Lic Extract	Pot marigold	Gharanjik F. et al., 2022
<i>Momordica charantia</i> L	Cucurbitaceae	Aqueous Extract	Bitter melon,	Hussain L. et al., 2022
<i>Aronia melanocarpa</i> (Michx.) Elliott	Rosaceae	Plant Extract	Black chokeberry	Rudic J. et al., 2022
<i>Ficus religiosa</i> L	Moraceae	Aqueous Extract	Peepal tree	Suriyakalaa et al., 2021
<i>Vernonia amygdalina</i> Delile	Asteraceae	Ethanollic Extract	Grawa	Ibeawuchi et al., 2021
<i>Withania coagulans</i> (Stocks) Dunal	Solanaceae	Aqueous Extract	Paneer phool	Ayaz H. et al., 2021
<i>Azadirachta indica</i> A.Juss.	Meliaceae	Ethanollic Extract	Neem, nimtree	Patel S.V. et al., 2021
<i>Peucedanum grande</i> C.B. Clarke	Apiaceae	Hydro alcoholic extract	Wild Carrot	Kausara F. et al., 2021
<i>Vitex agnus-castus</i> L.	Lamiaceae	Ethanollic extract	Chaste tree	Feyzollahi Z. et al., 2021
<i>Cicer arietinum</i> L.	Leguminosae	Seed ethanol extract	Chickpea	Ali S.E. et al., 2021
<i>Urtica dioica</i> L.	Urticaceae	Nettle extract	Stinging nettle	Bandariyan et al., 2021
<i>Ficus deltoidea</i> Jack	Moraceae	Methanollic extract	Mistletoe fig	Haslan Muhammad et al. , 2021
<i>Cuscuta reflexa</i> Roxb.	Convolvulaceae	Hydro alcoholic extract	Dodder	Kausara F. et al., 2021
<i>Actaea racemosa</i> L	Ranunculaceae	AR extracts	Black cohosh,	Azouz A.A. et al., 2021
<i>Nigella sativa</i> L.	Ranunculaceae	Hydro alcohol lic extract	Black caraway	Khani S. et al., 2021
<i>Origanum majorana</i> L.	Lamiaceae	Majoram extract	Sweet marjoram	Rababa'h A.M. et al., 2020
<i>Berberis integrerrima</i> Bunge	Berberidaceae	Hydro alcohol lic extract	Barberry	Ashkar F. et al., 2020

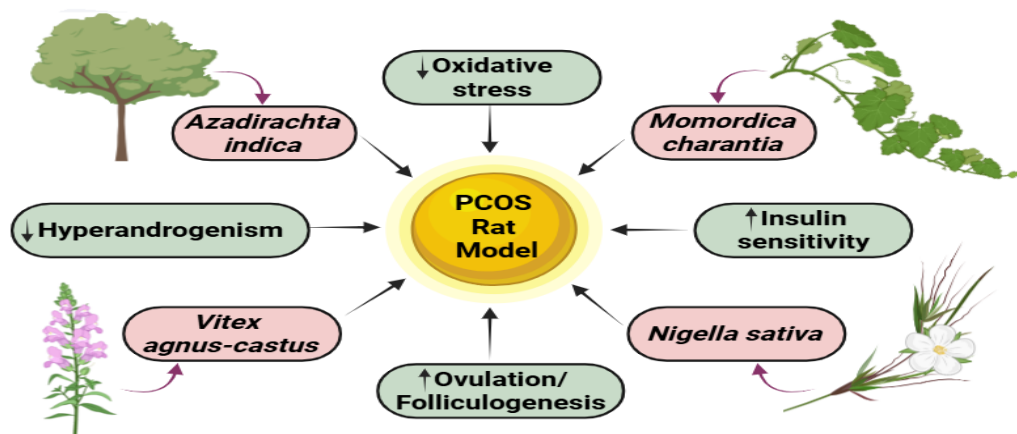


Figure 1. Graphical representation of medicinal plants, extracts, and their therapeutic roles in PCOS experimental models. Selected medicinal plants with hydroalcoholic, ethanolic, methanolic, and aqueous extracts have demonstrated therapeutic activity in PCOS rat models.”

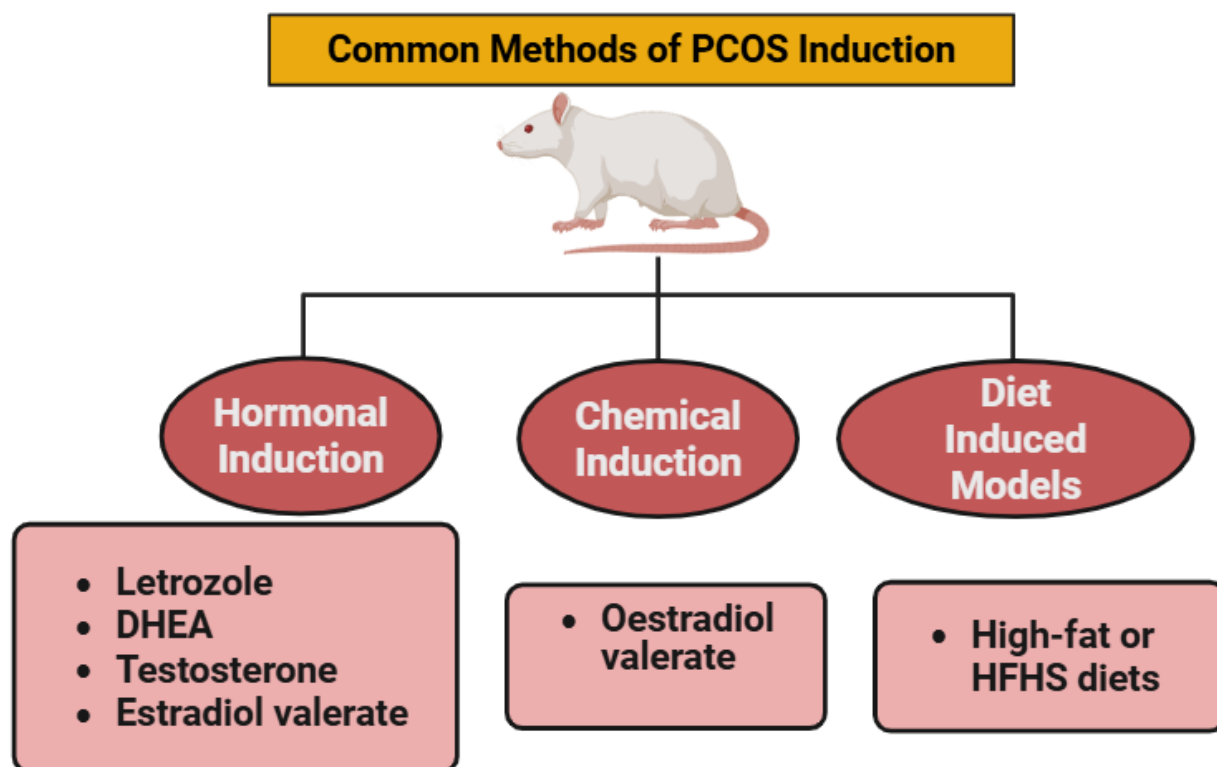


Figure.2. Schematic Representation of Common Methods for PCOS Induction in Rat Models

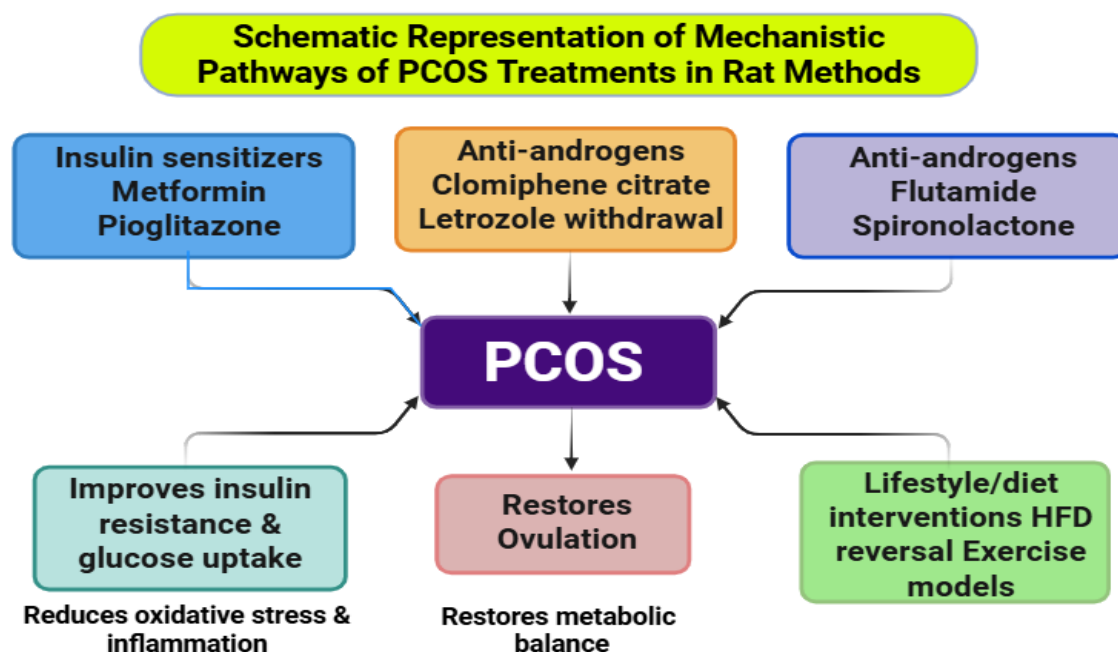


Figure.3. Schematic Representation of Metabolic Characteristics and Mechanistic Pathways in PCOS Rat Models

Chemical Induction

Although chemical induction frequently overlaps with hormonal approaches, it usually refers to nonsteroidal drugs like oestradiol valerate. A single EV dose is the most common chemical trigger for generating persistent oestrus and cystic ovarian morphology, however it has limitations in mimicking metabolic characteristics (Al-Dossary, et al.,2021).

Diet-Induced Models

Chronic consumption of **high-fat or high-fat/high-sucrose (HFHS)** diets has been demonstrated to cause reproductive and metabolic problems. Symptoms may include irregular cycles, polycystic ovarian morphology, insulin resistance, obesity, and dyslipidaemia (Bai, et al.,2024). HFHS diets are often combined with letrozole or DHEA to achieve a more clinically relevant phenotype (Poojary, et al.,2022). This makes diet-induced mice ideal for investigations investigating the metabolic problems of PCOS Figure 2.

Comparative Effectiveness of Induction Methods.

Letrozole, DHEA, TP, and EV consistently reproduce reproductive characteristics such as anovulation and cystic follicles. Letrozole and DHEA are the most commonly utilised, owing to their repeatability and closeness to human hyperandrogenic PCOS (Zhang, & Xu, 2022). Metabolic characteristics (insulin resistance, dyslipidaemia, obesity) are best recreated using diet-induced models or combination models (e.g., letrozole + HFD, DHEA + HFD). Hormonal induction alone may not be enough to detect metabolic syndrome (Lin, et al.,2021). Mechanistic congruence with human PCOS: aromatase inhibition (letrozole) and androgen excess (DHEA, TP) resemble the endocrine axis, while diet-induced models replicate the metabolic driver of PCOS. Therefore, selecting the induction approach should be directed by the primary study purpose (Somarathna et al.,2022).

Limitations of current models

Rat models of polycystic ovarian syndrome (PCOS) have various drawbacks that reduce their translational utility. Protocol variability, which includes variations in dose, duration, mode of

administration, and rat age or strain, limits reproducibility between trials Stokes et al.,2021. Moreover, individual models often provide only partial representation of PCOS: oestradiol valerate (EV) models capture ovulatory dysfunction but lack robust metabolic features, while androgenisation models effectively mimic reproductive endpoints but typically require dietary supplementation to induce metabolic traits (Di Berardino et al.,2022). Short induction durations, such as the regularly used 21-day letrozole procedure, make it difficult to simulate the chronic and lifelong character of PCOS, instead focussing on acute pathophysiological changes (Parker, 2023). Combination models that include hormones and high-fat diets can improve clinical relevance, but they bring confounding factors that make mechanistic interpretation difficult (Gupta et al.,2022). Finally, no one rat model can truly capture the variability of human PCOS, which ranges from lean to obese and includes a wide range of metabolic and mental comorbidities (Sarma et al.,2021).

Medicinal Plants Used in PCOS Treatment (in rats)

Herbal therapies tested in PCOS rat models rely on a few recurring phytochemical themes flavonoids, alkaloids, terpenoids, saponins, and polyphenols that produce complementary effects such as lowering androgen action, quenching oxidative stress/inflammation, improving insulin sensitivity, and restoring follicular development and ovulation (see mechanisms below). Several plants have been frequently examined in letrozole- or androgen-induced PCOS animals, providing a useful roadmap for preclinical phytomedicine research. (Indirani et al.,2026; Muthukumaran et al.,2026; Pagani, et al.,2024).

Discussion

Strengths and limitations of existing studies

PCOS research has advanced as a result of coordinated guideline formulation, mechanistic preclinical study, and increased genetic and clinical data collection. The 2023 International Evidence-Based Guideline harmonised diagnostic and management criteria while explicitly prioritising research issues, so increasing trial comparability

and directing clinically relevant outcome choices. (Tay, et al.,2025). Preclinical models (prenatal androgenisation, letrozole, DHT, DHEA) reproduce core reproductive and metabolic phenotypes— anovulation, polycystic ovarian morphology, LH dysregulation, and insulin resistance—and provide tractable platforms for testing causal hypotheses and candidate therapies (Das, et al., 2022; Ayyadurai et al., 2026; Anbazhagan et al.,2026).

Figure.3. However, there are some significant restrictions to translation. Phenotypic heterogeneity (inconsistent definitions of biochemical vs. clinical hyperandrogenism and ultrasound criteria), short follow-up periods, underpowered subgroup analyses, and limited ethnic/metabolic diversity continue to impede precision-medicine efforts and long-term risk assessment. (Johansso et al.,2023). Animal models, while mechanistically informative, do not represent the complete spectrum of human PCOS endotypes and frequently focus on a single pathogenic axis (e.g., androgen excess) without accounting for comorbidities such as sleep difficulties or neuropsychiatric symptoms. Direct extrapolation is further limited by species differences in folliculogenesis, steroid metabolism, and hypothalamic-pituitary control. (Das, et al.,2023).

Translational significance of animal studies to humans

Animal studies have been critical in demonstrating that androgen excess might be sufficient to produce reproductive and metabolic failure, bolstering causal theories that relate hyperandrogenism to insulin resistance and ovarian function. Rodent letrozole and prenatal-androgen models recapitulate many of the characteristics reported in women with PCOS, and they allow for experimental modification of timing, dose, and environmental modifiers (e.g., a high-fat diet) to investigate interactions that would be impractical or unethical in people. (King, 2024). However, translational constraints must be acknowledged: interspecies variations (ovarian cycle dynamics, steroid biotransformation, and neuroendocrine regulation) can influence phenotype expression and medication reactions. The most productive translational strategy is triangulation, which involves using multiple complementary animal

models mapped to defined human endotypes, as well as human cell/tissue models (primary theca/granulosa cells, adipose explants, organoids) and human observational/interventional studies to validate mechanistic hypotheses. (Bortoletto, et al., 2023).

Research gaps and Future Directions

Standardise phenotypes and outcomes. Use core outcome sets (reproductive, metabolic, mental-health, and pregnancy) across trials and observational cohorts to allow for pooled analyses and endotype-specific conclusions. Guideline groups have already emphasised these themes and provided a framework for harmonisation (Hogervorst et al.,2023). Move beyond GWAS locus discovery to functional genomics (CRISPR perturbation in human organoids, single-cell multi-omics of ovary/adipose/hypothalamus) to connect risk variants to cellular phenotypes and druggable pathways (Karagiannakos et al.,2022; Sudhakaran et al., 2026; Renukadevi et al., 2026). Longitudinal and intergenerational cohorts. Increase follow-up to study cardiometabolic outcomes, pregnancy problems, and offspring health; research how mother metabolic/endocrine status and therapies affect foetal programming (Grilo et al.,2022). Refine preclinical models. Use matched model panels (e.g., prenatal androgen + diet-induced obesity) to simulate specific human endotypes and evaluate therapies in a setting similar to comorbid conditions. Integrate humanised and organoid systems to reduce species-translation uncertainties (Berridge et al.,2024). Conduct pragmatic head-to-head trials of lifestyle, first-line ovulation induction (letrozole), insulin-sensitizers (metformin, berberine), and promising phytotherapies, incorporating patient-reported outcomes, cost-effectiveness, and equity analyses López-Cabanillas (Lomelí et al., 2024).

Conclusions:

Polycystic ovarian syndrome (PCOS) is a complicated condition that includes not only reproductive issues but also metabolic, endocrine, and psychological issues. Rat models have significantly contributed to the understanding of the complex pathophysiology of polycystic ovarian syndrome (PCOS) and the assessment of treatment

strategies. Diet-induced models, testosterone, oestradiol valerate, DHEA, and letrozole have all been efficient in replicating specific characteristics of human polycystic ovarian syndrome (PCOS); however, no single induction method has successfully included the entirety of the condition's heterogeneity. Medicinal plants are appealing alternatives or additions to standard treatments because they are antioxidants, anti-inflammatories, insulin-sensitizers, and hormone-modulators. Studies on many botanicals, such as ashwagandha, cinnamon, turmeric, and fenugreek, have demonstrated their efficacy in restoring ovarian morphology, enhancing oestrous cyclicity, reducing androgen excess, and ameliorating metabolic disorders.

The complexity of human PCOS endotypes, interspecies variations, and the diversity of induction methodologies present significant challenges in translating animal research findings into therapeutic applications, notwithstanding these advancements. Future research should concentrate on the integration of preclinical data with human trials, the standardisation of outcome metrics, and the enhancement of animal models to more accurately reflect comorbidities. Combining phytotherapy with current management strategies holds significant potential for developing safe, cost-effective, and comprehensive treatments for polycystic ovarian syndrome (PCOS). To improve long-term reproductive and metabolic outcomes for women with PCOS, we will need to combine new research findings with what we now know about how to treat them.

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Authors' contributions:

ATM conceived the research, assisted in its design, execution, and analysis, as well as data

interpretation and manuscript writing. AT, and BG, BA and GA was involved in the study's design, planning, data processing, and interpretation, as well as proofreading the manuscript. The manuscript was written by both contributors, who also provided feedback. The final manuscript has been read by all writers and authorised.

Data availability:

The corresponding author will provide the datasets produced and/or analysed during the current work upon appropriate request.

Declarations: Conflict of interest The authors declare no competing interests.

Ethical approval : Not applicable.

References

- [1] Abtahi-Eivari, S. H., Moghimian, M., Soltani, M., Shoorei, H., Asghari, R., Hajizadeh, H., & Ghaderi, F. K. (2018). The effect of *Galega officinalis* on hormonal and metabolic profile in a rat model of polycystic ovary syndrome. *International Journal of Womens Health and Reproduction Sciences*, 6(3), 276-282.
- [2] Adelakun, S. A., Ojewale, A. O., Jeje, S. O., & Adedotun, O. A. (2022). Histomorphometric and biochemical activities of bioactive component of *Cyperus esculentus* tubers extract on letrozole-induced polycystic ovarian syndrome and cholesterol homeostasis in female Sprague-Dawley rats. *Toxicology Research and Application*, 6, 23978473221109475.
- [3] Adelakun, S. A., Ukwenya, V. O., Peter, A. B., Siyanbade, A. J., & Akinwumiju, C. O. (2022). Therapeutic effects of aqueous extract of bioactive active component of *Ageratum conyzoides* on the ovarian-uterine and hypophysis-gonadal axis in rat with polycystic ovary syndrome: Histomorphometric evaluation and biochemical assessment. *Metabolism Open*, 15, 100201. <https://doi.org/10.1016/j.metop.2022.100201>
- [4] Al Raish, S. M., Almasri, R. S., Bedir, A. S., & Elkahwagy, A. A. (2025). Phytochemical Composition, Bioactive Compounds, and Antidiabetic Potential of Four Medicinal Plants Native to the UAE: *Capparis spinosa*, *Citrullus colocynthis*, *Morus alba*, and *Rhazya stricta*. *Biology*, 14(9), 1146.
- [5] Alahmadi, A. A., Alzahrani, A. A., Ali, S. S., Alahmadi, B. A., Arab, R. A., & El-Shitany, N. A. E. A. (2020). Both *Matricaria chamomilla* and metformin extract

- improved the function and histological structure of thyroid gland in polycystic ovary syndrome rats through antioxidant mechanism. *Biomolecules*, 10(1), 88. <https://doi.org/10.3390/biom10010088>
- [6] Al-Dossary, A. A., Tawfik, E. A., Isichei, A. C., Sun, X., Li, J., Alshehri, A. A., ... & Almalik, A. M. (2021). Engineered EV-mimetic nanoparticles as therapeutic delivery vehicles for high-grade serous ovarian cancer. *Cancers*, 13(12), 3075.
- [7] Ali, S. E., El Badawy, S. A., Elmosalamy, S. H., Emam, S. R., Azouz, A. A., Galal, M. K., ... & Hassan, B. B. (2021). Novel promising reproductive and metabolic effects of Cicer arietinum L. extract on letrozole induced polycystic ovary syndrome in rat model. *Journal of Ethnopharmacology*, 278, 114318.
- [8] Ali, S. E., El Badawy, S. A., Elmosalamy, S. H., Emam, S. R., Azouz, A. A., Galal, M. K., & Hassan, B. B. (2021). Novel promising reproductive and metabolic effects of Cicer arietinum L. extract on letrozole induced polycystic ovary syndrome in rat model. *Journal of Ethnopharmacology*, 278, 114318. <https://doi.org/10.1016/j.jep.2021.114318>
- [9] Alizadeh, F., Ramezani, M., & Piravar, Z. (2020). Effects of Stachys sylvatica hydroalcoholic extract on the ovary and hypophysis-gonadal axis in a rat with polycystic ovary syndrome. *Middle East Fertility Society Journal*, 25(1), 4. <https://doi.org/10.1186/s43043-020-0015-9>
- [10] Anbazhagan, V., Natrajan, A., Arul, J. et al. Strategic development of a buffalo farming framework and optimization of the foraging behaviour using mathematical models. *Trop Anim Health Prod* 58, 424 (2026). <https://doi.org/10.1007/s11250-026-05211-6>.
- [11] Asghari, R., Shokri-Asl, V., Rezaei, H., Tavallaie, M., Khafaei, M., Abdolmaleki, A., & Seghinsara, A. M. (2021). Alteration of TGFB1, GDF9, and BMPR2 gene expression in preantral follicles of an estradiol valerate-induced polycystic ovary mouse model can lead to anovulation, polycystic morphology, obesity, and absence of hyperandrogenism. *Clinical and experimental reproductive medicine*, 48(3), 245.
- [12] Ashkar, F., Eftekhari, M. H., Tanideh, N., Koohpeyma, F., Mokhtari, M., Irajie, C., & Irajie, A. (2020). Effect of hydroalcoholic extract of Berberis integerrima and resveratrol on ovarian morphology and biochemical parameters in Letrozole-induced polycystic ovary syndrome rat model: an experimental study. *International Journal of Reproductive Biomedicine*, 18(8), 637. <https://doi.org/10.18502/ijrm.v13i8.7505>
- [13] Ashkar, F., Eftekhari, M. H., Tanideh, N., Koohpeyma, F., Mokhtari, M., Irajie, C., & Irajie, A. (2020). Effect of hydroalcoholic extract of Berberis integerrima and resveratrol on ovarian morphology and biochemical parameters in Letrozole-induced polycystic ovary syndrome rat model: An experimental study. *International journal of reproductive biomedicine*, 18(8), 637.
- [14] Atashpour, S., Jahromi, H. K., Jahromi, Z. K., & Maleknasab, M. (2017). Comparison of the effects of ginger extract with clomiphene citrate on sex hormones in rats with polycystic ovarian syndrome. *International Journal of Reproductive BioMedicine*, 15(9), 561.
- [15] Ayaz, H., Anjum, A. F., Nasar Abbas Shamsi, A. S., Arshad, S., Khokhar, A., & Laique, T. Effect of Aqueous Extract of Withania Coagulans and Metformin on Gonadotropin Levels in Polycystic Ovarian Rats.
- [16] Ayyadurai, T., Mohan, P. K., Annamalai, A., Kamaraj, C., & Waheeb, M. Q. (2026). Biogenic silver nanoparticles synthesis from Guilandina bonduc L. seed kernel extract with antibacterial, antioxidant and anticancer potential against ovarian Cancer cells. *Results in Chemistry*, 103246.
- [17] Ayyadurai, T., Moola, A. K., Mohan, P. K., Thirupathi, S. K., Shanmugam, A., & Bollipo Diana, R. K. (2022). Ameliorative effects of Guilandina bonduc L. aqueous seed extract on letrozole induced polycystic ovary syndrome in female wistar albino rats. *Advances in Traditional Medicine*, 22(4), 885-903.
- [18] Ayyadurai, T., Ravi, S., & Annamalai, A. (2026). Steroidogenic Enzyme Dysregulation in Polycystic Ovary Syndrome: Mechanistic Insights and Emerging Therapeutic Strategies. *The Journal of Steroid Biochemistry and Molecular Biology*, 107088.
- [19] Azouz, A. A., Ali, S. E., Abd-Elsalam, R. M., Emam, S. R., Galal, M. K., Elmosalamy, S. H., ... & El Badawy, S. A. (2021). Modulation of steroidogenesis by Actaea racemosa and vitamin C combination, in letrozole induced polycystic ovarian syndrome rat model: promising activity without the risk of hepatic adverse effect. *Chinese Medicine*, 16(1), 36.
- [20] Bai, H., Ding, H., & Wang, M. (2024). Polycystic ovary syndrome (PCOS): symptoms, causes, and treatment. *Clinical and Experimental Obstetrics & Gynecology*, 51(5), 126.
- [21] Bandariyan, E., Mogheiseh, A., & Ahmadi, A. (2021). The effect of lutein and Urtica dioica extract on in vitro production of embryo and oxidative status in polycystic ovary syndrome in a model of mice. *BMC Complementary Medicine and Therapies*, 21, 1-11. <https://doi.org/10.1186/s12906-021-03229-x>

- [22] Bandariyan, E., Mogheiseh, A., & Ahmadi, A. (2021). The effect of lutein and *Urtica dioica* extract on in vitro production of embryo and oxidative status in polycystic ovary syndrome in a model of mice. *BMC Complementary Medicine and Therapies*, 21, 1-11.
- [23] Barzegar, M. H., Khazali, H., Kalantar, S. M., & Khoradmehr, A. (2017). Effect of *Citrullus colocynthis* hydro-alcoholic extract on hormonal and folliculogenesis process in estradiol valerate-induced PCOs rats model: An experimental study. *International Journal of Reproductive BioMedicine*, 15(10), 661.
- [24] Basak, S., Varma, S., & Duttaroy, A. K. (2023). Modulation of fetoplacental growth, development and reproductive function by endocrine disrupters. *Frontiers in Endocrinology*, 14, 1215353.
- [25] Benitez, A., Riquelme, R., Del Campo, M., Araya, C., & Lara, H. E. (2021). Nerve growth factor: a dual activator of noradrenergic and cholinergic systems of the rat ovary. *Frontiers in Endocrinology*, 12, 636600.
- [26] Berridge, B., Pierson, J., Pettit, S., & Stockbridge, N. (2024). Challenging the status quo: a framework for mechanistic and human-relevant cardiovascular safety screening. *Frontiers in Toxicology*, 6, 1352783.
- [27] Bortoletto, R., Piscitelli, F., Candolo, A., Bhattacharyya, S., Balestrieri, M., & Colizzi, M. (2023). Questioning the role of palmitoylethanolamide in psychosis: a systematic review of clinical and preclinical evidence. *Frontiers in Psychiatry*, 14, 1231710.
- [28] Cazzola, R., Della Porta, M., Piuri, G., & Maier, J. A. (2024). Magnesium: A defense line to mitigate inflammation and oxidative stress in adipose tissue. *Antioxidants*, 13(8), 893.
- [29] Chang, K. J., Chen, J. H., & Chen, K. H. (2024). The pathophysiological mechanism and clinical treatment of polycystic ovary syndrome: A molecular and cellular review of the literature. *International journal of molecular sciences*, 25(16), 9037.
- [30] Das, P. K., Mukherjee, J., & Banerjee, D. (2023). Female reproductive physiology. In *Textbook of veterinary physiology* (pp. 513-568). Singapore: Springer Nature Singapore.
- [31] Das, S., Taylor, K., Kozubek, J., Sardell, J., & Gardner, S. (2022). Genetic risk factors for ME/CFS identified using combinatorial analysis. *Journal of Translational Medicine*, 20(1), 598.
- [32] Desai, B. N., Maharjan, R. H., & Nampoothiri, L. P. (2012). *Aloe barbadensis* Mill. formulation restores lipid profile to normal in a letrozole-induced polycystic ovarian syndrome rat model. *Pharmacognosy Research*, 4(2), 109. <https://doi.org/10.4103/0974-8490.94736>
- [33] Dhanka, S., Kumar, A., Sharma, A., Vundavilli, H., Maini, S., & Rajasekhar, E. (2025). Advances in Machine Learning and Deep Learning for Hormonal Disorder Diagnosis: an Exhaustive Review on PCOS, Thyroid, and Optimization Techniques. *Archives of Computational Methods in Engineering*, 1-45.
- [34] Di Berardino, C., Peserico, A., Capacchietti, G., Zappacosta, A., Bernabò, N., Russo, V., ... & Barboni, B. (2022). High-fat diet and female fertility across lifespan: a comparative lesson from mammal models. *Nutrients*, 14(20), 4341.
- [35] Dou, L., Zheng, Y., Li, L., Gui, X., Chen, Y., Yu, M., & Guo, Y. (2018). The effect of cinnamon on polycystic ovary syndrome in a mouse model. *Reproductive Biology and Endocrinology*, 16, 1-10. <https://doi.org/10.1186/s12958-018-0418-y>
- [36] Dutta, R., Eramma, N., Renuka, J. S., & Patil, S. J. Effect of Nutri-Spices on Fertility and Sexual Dysfunctions. In *Nutraceuticals for the Treatment and Prevention of Sexual Disorders* (pp. 367-398).
- [37] Feyzollahi, Z., Kouchesfehiani, H. M., Jalali, H., Eslimi-Esfahani, D., & Hosseini, A. S. (2021). Effect of *Vitex agnus-castus* ethanolic extract on hypothalamic KISS-1 gene expression in a rat model of polycystic ovary syndrome. *Avicenna journal of phytomedicine*, 11(3), 292. 40.
- [38] Gao, J., Huang, Y., Song, Y., Huang, X., Zhang, D., & Hou, Z. (2024). Therapeutic effects of *Althaea officinalis* L. and metformin on Estradiol-induced polycystic ovary syndrome in rats: insights into the PI3K/AKT pathway, inflammation, and oxidative stress. *Cell Journal (Yakhteh)*, 26(8), 473-486.
- [39] Gharanjik, F., Shojaeifard, M. B., Karbalaee, N., & Nemati, M. (2022). The Effect of Hydroalcoholic *Calendula Officinalis* Extract on Androgen-Induced Polycystic Ovary Syndrome Model in Female Rat. *BioMed Research International*, 2022(1), 7402598.
- [40] Gharanjik, F., Shojaeifard, M. B., Karbalaee, N., & Nemati, M. (2022). The Effect of Hydroalcoholic *Calendula Officinalis* Extract on Androgen-Induced Polycystic Ovary Syndrome Model in Female Rat. *BioMed research international*, 2022.
- [41] Grilo, L. F., Diniz, M. S., Tocantins, C., Areia, A. L., & Pereira, S. P. (2022). The Endocrine–Metabolic Axis Regulation in Offspring Exposed to Maternal Obesity—Cause or Consequence in Metabolic Disease Programming?. *Obesities*, 2(3), 236-255.
- [42] Guo, F., Gong, Z., Fernando, T., Zhang, L., Zhu, X., & Shi, Y. (2022). The lipid profiles in different

- characteristics of women with PCOS and the interaction between dyslipidemia and metabolic disorder states: a retrospective study in Chinese population. *Frontiers in Endocrinology*, 13, 892125.
- [43] Gupta, C., Chandrashekar, P., Jin, T., He, C., Khullar, S., Chang, Q., & Wang, D. (2022). Bringing machine learning to research on intellectual and developmental disabilities: taking inspiration from neurological diseases. *Journal of neurodevelopmental disorders*, 14(1), 28.
- [44] Hachem, S., Al Battal, M., Dakdouk, H., Natour, D. E., & Borjac, J. (2025). Anti-Inflammatory and Antioxidant Effects of Gundelia tournefortii Aqueous Extract on the Liver and Kidney of PCOS Mice. *Journal of Evidence-Based Integrative Medicine*, 30, <https://doi.org/10.1177/2515690X241304519>
- [45] Hamza, A. H., AlBishri, W. M., & Alfaris, M. H. (2019). Effect of Vitex agnus-castus plant extract on polycystic ovary syndrome complications in experimental rat model. *Asian Pacific Journal of Reproduction*, 8(2), 63-69. <https://doi.org/10.4103/2305-0500.254647>
- [46] Haslan, M. A., Samsulrizal, N., Hashim, N., Zin, N. S. N. M., Shirazi, F. H., & Goh, Y. M. (2021). Ficus deltoidea ameliorates biochemical, hormonal, and histomorphometric changes in letrozole-induced polycystic ovarian syndrome rats. *BMC Complementary Medicine and Therapies*, 21, 1-13.
- [47] Hogervorst, M. A., Møllebæk, M., Vreman, R. A., Lu, T. A., Wang, J., De Bruin, M. L., ... & Goettsch, W. (2023). Perspectives on how to build bridges between regulation, health technology assessment and clinical guideline development: a qualitative focus group study with European experts. *BMJ open*, 13(8), e072309.
- [48] Hoseinpour, M. J., Ghanbari, A., Azad, N., Zare, A., Abdi, S., Sajadi, E., & Abdollahifar, M. A. (2019). Ulmus minor bark hydro-alcoholic extract ameliorates histological parameters and testosterone level in an experimental model of PCOS rats. *Endocrine Regulations*, 53(3), 146-153.
- [49] Hussain, L., Aamir, N., Hussain, M., Asif, M., Chauhdary, Z., Manzoor, F., & Riaz, M. (2022). Therapeutic investigation of standardized aqueous methanolic extract of bitter melon (*Momordica charantia* L.) for its potential against polycystic ovarian syndrome in experimental animals' model: in vitro and in vivo studies. *Evidence-Based Complementary and Alternative Medicine*, 2022(1), 5143653. <https://doi.org/10.1155/2022/5143653>
- [50] Hussain, L., Aamir, N., Hussain, M., Asif, M., Chauhdary, Z., Manzoor, F., ... & Riaz, M. (2022). Therapeutic Investigation of Standardized Aqueous Methanolic Extract of Bitter Melon (*Momordica charantia* L.) for Its Potential against Polycystic Ovarian Syndrome in Experimental Animals' Model: In Vitro and In Vivo Studies. *Evidence-Based Complementary and Alternative Medicine*, 2022.
- [51] Ibeawuchi, I. C. (2021). Ameliorative Effect of Ethanoic Extract of Vernonia amygdalina (Del) Leaves on Reproductive Functions of Letrozole-induced Polycystic Ovarian Syndrome in Wistar Rats.
- [52] Indirani, M., Sudheer, S., Mahaveerakannan, R., & Ruba, P. (2026). Gallstone Disease Prediction Using Clinical and Biochemical Features Through Ensemble Learning Techniques. *International Journal of Computational Intelligence Systems*, 19(1), 19.
- [53] Jancyhelan, J., Thirumurugan, A., Alagumanian, S., & Vignesh, K. (2026). Eco-friendly biosynthesis of silver nanoparticles using marine algal extract and their biomedical applications. *Results in Chemistry*, 103606.
- [54] Jelodar, G., Masoomi, S., & Rahmanifar, F. (2018). Hydroalcoholic extract of flaxseed improves polycystic ovary syndrome in a rat model. *Iranian Journal of Basic Medical Sciences*, 21(6), 645. <https://doi.org/10.22038/ijbms.2018.25778.6349>
- [55] Johansson, Å., Andreassen, O. A., Brunak, S., Franks, P. W., Hedman, H., Loos, R. J., ... & Jacobsson, B. (2023). Precision medicine in complex diseases—Molecular subgrouping for improved prediction and treatment stratification. *Journal of internal medicine*, 294(4), 378-396.
- [56] Joy, F. O. F., Kelechukwu, U. Z., James, A., Adebayo, I. A., Opeyem, F., Oluyemi, A. A., & Susan, A. T. (2022). Selected Toxicity Study on Ethanolic Extract of Ocimum gratissimum (Linn.) Leaves in Letrozole-Induced Polycystic Ovarian Syndrome in Wistar Rats. *The Journal of Phytopharmacology*, 11(3), 142-146.
- [57] Jung, J. H., Park, H. T., Kim, T., Jeong, M. J., Lim, S. C., Nah, S. Y., & Bae, C. S. (2011). Therapeutic effect of korean red ginseng extract on infertility caused by polycystic ovaries. *Journal of Ginseng Research*, 35(2), 250.
- [58] Kalimuthu, V., Chandran Manimegalai, S., Venkatesan, R., Krishnamoorthy, S. P., Dey, N., Ramesh, T., & Balamuthu, K. (2025). Exploring the Therapeutic Potential of Terminalia chebula Retz. in Alleviating the Complications of Letrozole-Induced PCOS in Rat Model. *Reproductive Sciences*, 32(3), 836-853.
- [59] Karagiannakos, A., Adamaki, M., Tsintarakis, A., Vojtesek, B., Fähræus, R., Zoumpourlis, V., & Karakostis, K. (2022). Targeting oncogenic pathways

- in the era of personalized oncology: a systemic analysis reveals highly mutated signaling pathways in cancer patients and potential therapeutic targets. *Cancers*, 14(3), 664.
- [60] Karthikeyan, M., Sabarathinam, S., Mohan, H., & Usha, B. (2025). An integrated network pharmacological approach unveils the therapeutic mechanism of bonducellin, a homoisoflavonoid from *Caesalpinia bonducella*, against polycystic ovary syndrome. *Tradit Med Res*, 10(11), 65.
- [61] Kausar, F., Rather, M. A., Bashir, S. M., Alsaffar, R. M., Nabi, S. U., Ali, S. I., ... & Wali, A. F. (2021). Ameliorative effects of *Cuscuta reflexa* and *Peucedanum grande* on letrozole induced polycystic ovary syndrome in Wistar rats. *Redox Report*, 26(1), 94-104.
- [62] Kausar, F., Rather, M. A., Bashir, S. M., Alsaffar, R. M., Nabi, S. U., Ali, S. I., ... & Wali, A. F. (2021). Ameliorative effects of *Cuscuta reflexa* and *Peucedanum grande* on letrozole induced polycystic ovary syndrome in Wistar rats. *Redox Report*, 26(1), 94-104.
- [63] Ke, Y., Tang, D., Yang, Q., Zhao, H., Zheng, J., & Zhu, C. (2025). Anti-Müllerian hormone in PCOS: Molecular regulation and emerging therapeutic strategies. *Biomolecules and Biomedicine*.
- [64] Khaled, N., El-Bahy, A. A., Radwan, R., Handoussa, H., & AbdelMaksoud, S. (2019). *Ocimum kilimandscharicum* L. restores ovarian functions in letrozole-induced Polycystic Ovary Syndrome (PCOS) in rats: Comparison with metformin. *Life Sciences*, 232, 116640.
- [65] Khani, S., Abdollahi, M., Khalaj, A., Heidari, H., & Zohali, S. (2021). The effect of hydroalcoholic extract of *Nigella Sativa* seed on dehydroepiandrosterone-induced polycystic ovarian syndrome in rats: An experimental study. *International Journal of Reproductive BioMedicine*, 19(3), 271.
- [66] Khani, S., Abdollahi, M., Khalaj, A., Heidari, H., & Zohali, S. (2021). The effect of hydroalcoholic extract of *Nigella Sativa* seed on dehydroepiandrosterone-induced polycystic ovarian syndrome in rats: An experimental study. *International Journal of Reproductive BioMedicine*, 19(3), 271.
- [67] Khodaeifar, F., Fazljou, S. B., Khaki, A., Torbati, M., Madarek, E. O. S., Khaki, A. A., & Dalili, A. H. (2019). Investigating the role of hydroalcoholic extract of *Apium graveolens* and *Cinnamon zeylanicum* on metabolically change and ovarian oxidative injury in a rat model of polycystic ovary syndrome. *International Journal of Womens Health Reproductive Science*, 7(1), 92-98.
- [68] King, A. (2024). *Genotype-based diet and physical activity advice: effects on behaviour change to reduce risk factors for cardiometabolic disease* (Doctoral dissertation, St Mary's University).
- [69] Kiran, Z. (2024). Diagnostic criteria for polycystic ovary syndrome. In *Polycystic Ovary Syndrome* (pp. 61-74).
- [70] Lee, Y. H., Yang, H., Lee, S. R., Kwon, S. W., Hong, E. J., & Lee, H. W. (2018). Welsh onion root (*Allium fistulosum*) restores ovarian functions from letrozole induced-polycystic ovary syndrome. *Nutrients*, 10(10), 1430.
- [71] Li, H., Liu, Y., Wang, Y., Zhao, X., & Qi, X. (2021). Hormone therapy for ovarian cancer: Emphasis on mechanisms and applications. *Oncology reports*, 46(4), 1-27.
- [72] Li, P., Xie, L., Zheng, H., Feng, Y., Mai, F., Tang, W., ... & Chen, X. (2025). Gut microbial-derived 3, 4-dihydroxyphenylacetic acid ameliorates reproductive phenotype of polycystic ovary syndrome. *iMeta*, e70065.
- [73] Lin, W., Wen, L., Wen, J., & Xiang, G. (2021). Effects of sleeve gastrectomy on fecal gut microbiota and short-chain fatty acid content in a rat model of polycystic ovary syndrome. *Frontiers in endocrinology*, 12, 747888.
- [74] Liu, J. C., Zou, Y. J., Zhang, K. H., Ji, Y. M., Wang, Y., & Sun, S. C. (2025). Proteomic analysis reveals the alleviation of follicular development defects in offspring mice under DEHP exposure by melatonin. *BMC biology*, 23(1), 65.
- [75] López-Cabanillas Lomeli, M., Tijerina-Sáenz, A., García-Hernández, D. G., Hernández-Salazar, M., Salas García, R., González-Llerena, J. L., ... & Heya, M. S. (2024). Colon Cancer: Overview on Improved Therapeutic Potential of Plant-Based Compounds Using Nanotechnology. *Scientia Pharmaceutica*, 93(1), 1.
- [76] Madamsetty, T. (2025). Exploring herbal alternatives to pharmaceutical treatments for Polycystic Ovary Syndrome. *Journal of High School Science*, 9(3), 148-181.
- [77] Mahmoud, A. A., Elfiky, A. M., & Abo-Zeid, F. S. (2022). The anti-androgenic effect of quercetin on hyperandrogenism and ovarian dysfunction induced in a dehydroepiandrosterone rat model of polycystic ovary syndrome. *Steroids*, 177, 108936.
- [78] Manneras, L., Fazliana, M., Nazaimoon, W. W., Lonn, M., Gu, H. F., Ostenson, C. G., & Stener-Victorin, E. (2010). Beneficial metabolic effects of the Malaysian

- herb *Labisia pumila* var. *alata* in a rat model of polycystic ovary syndrome. *Journal of Ethnopharmacology*, 127(2), 346-351. <https://doi.org/10.1016/j.jep.2009.10.032>
- [79] Maulenkul, T., Kuandyk, A., Makhadiyeva, D., Dautova, A., Terzic, M., Oshibayeva, A., ... & Sarria-Santamera, A. (2024). Understanding the impact of endometriosis on women's life: an integrative review of systematic reviews. *BMC women's health*, 24(1), 524.
- [80] Meenaloshini, P., Thirumurugan, A., Achiraman, S., & Kumar, T. S. (2025). Protective effect of hydroalcoholic *Crateva religiosa* G. Forst. bark extract on oxidative stress, hormonal imbalance and gene expressions (CYP19A1 and PPAR γ) in letrozole-induced polycystic ovarian syndrome rats. *Journal of Ethnopharmacology*, 353, 120354.
- [81] Meera, B., Muralidharan, P., & Hari, R. (2021). Antioxidant potential of *Caesalpinia bonducella* seeds in the management of polycystic ovary syndrome (PCOS) using mifepristone induced rats model. *Journal of Herbs, Spices & Medicinal Plants*, 27(2), 123-134. <https://doi.org/10.1080/10496475.2020.1795041>
- [82] Morsi, A. A., Mersal, E. A., Farrag, A. R. H., Abdelmoneim, A. M., Abdelmenem, A. M., & Salim, M. S. (2022). Histomorphological changes in a rat model of polycystic ovary syndrome and the contribution of *Stevia* leaf extract in modulating the ovarian fibrosis, VEGF, and TGF- β immunoexpressions: Comparison with metformin. *Acta Histochemica et Cytochemica*, 55(1), 9-23.
- [83] Moshfegh, F., Balanejad, S. Z., Shahrokhaby, K., & Attaranzadeh, A. (2022). *Crocus sativus* (saffron) petals extract and its active ingredient, anthocyanin improves ovarian dysfunction, regulation of inflammatory genes and antioxidant factors in testosterone-induced PCOS mice. *Journal of Ethnopharmacology*, 282, 114594. <https://doi.org/10.1016/j.jep.2021.114594>
- [84] Mukherjee, A. G., Wanjari, U. R., Kannampuzha, S., Murali, R., Namachivayam, A., Ganesan, R., ... & Gopalakrishnan, A. V. (2023). The implication of mechanistic approaches and the role of the microbiome in polycystic ovary syndrome (PCOS): a review. *Metabolites*, 13(1), 129
- [85] Mukul Shyam, Aleen Veronica, Jyoti Wadhwa, Vidhi Sharma, Oveyaa B M, Prathap Srirangan, Rajendran Venkatesh, Sabina Evan Prince. FOXO transcription factors in Alzheimer's Disease: balancing neuroprotection and neuronal degeneration. *Molecular Biology Reports* (2026) 53:833. <https://doi.org/10.1007/s11033-026-12021-4>
- [86] Muthukumaran, D., Anitha, V., Baskar, G., & Shanmugam, R. (2026). Polycystic ovarian syndrome-Exploring the therapeutic and biomedical insights into the role of silver nanoparticles. *The Journal of Steroid Biochemistry and Molecular Biology*, 259, 106968.
- [87] Mvondo, M. A., Mzemdem Tsoplack, F. I., Awounfack, C. F., & Njamen, D. (2020). The leaf aqueous extract of *Myrianthus arboreus* P. Beauv.(Cecropiaceae) improved letrozole-induced polycystic ovarian syndrome associated conditions and infertility in female Wistar rats. *BMC Complementary Medicine and Therapies*, 20, 1-13.
- [88] Negi, N., & Sharma, I. (2025). Establishing PCOS in Wistar rats: A reliable model for understanding polycystic ovary syndrome: PCOS in Wistar rats as model organism. *Indian Journal of Experimental Biology (IJEb)*, 63(04), 301-311.
- [89] Pachiappan, S., Ramalingam, K., & Balasubramanian, A. (2021). Combined effects of *Gymnema sylvestre* and *Pergularia daemia* on letrozole-induced polycystic ovarian syndrome in rats. *Asian Pacific Journal of Reproduction*, 10(2), 68-74. <https://doi.org/10.4103/2305-0500.311610>
- [90] Pagani, E., Ropke, C. D., Soares, C. M., Perez, S. A. C., Benevides, P. J. C., Barbosa, B. S., ... & Behrens, M. D. (2024). Technology readiness level roadmap for developing innovative herbal medicinal products. *Pharmaceuticals*, 17(6), 703.
- [91] Parker, J. (2023). Pathophysiological effects of contemporary lifestyle on evolutionary-conserved survival mechanisms in polycystic ovary syndrome. *Life*, 13(4), 1056.
- [92] Patel, S. V., Maru, H., Chavda, V. K., Shah, J. N., & Patel, S. S. (2021). Ethanolic extract of *Azadirachta indica* ameliorates ovarian defects through phosphoinositide-3 kinase inhibition in a rat model of polycystic ovary syndrome. *Asian Pacific Journal of Reproduction*, 10(1), 21.
- [93] Pieczyńska, J. M., Pruszyńska-Oszmałek, E., Kołodziejcki, P. A., Łukomska, A., & Bajerska, J. (2022). The role of a high-fat, high-fructose diet on letrozole-induced polycystic ovarian syndrome in prepubertal mice. *Nutrients*, 14(12), 2478.
- [94] Poojary, P. S., Nayak, G., Panchanan, G., Rao, A., Kundapur, S. D., Kalthur, S. G., ... & Kalthur, G. (2022). Distinctions in PCOS induced by letrozole vs dehydroepiandrosterone with high-fat diet in mouse model. *Endocrinology*, 163(9), bqac097.
- [95] Rababa'h, A. M., Matani, B. R., & Ababneh, M. A. (2020). The ameliorative effects of marjoram in dehydroepiandrosterone induced polycystic ovary

- syndrome in rats. *Life Sciences*, 261, 118353. <https://doi.org/10.1016/j.lfs.2020.118353>
- [96] Rababa'h, A. M., Matani, B. R., & Ababneh, M. A. (2020). The ameliorative effects of marjoram in dehydroepiandrosterone induced polycystic ovary syndrome in rats. *Life sciences*, 261, 118353.
- [97] Radha, M., & Laxmipriya, N. (2016). Efficacy of non-polar extract (NPE) of *Aloe barbadensis* mill. in polycystic ovarian syndrome (PCOS) rodent model-an "in vivo" study. *International Journal of Pharmaceutical Sciences and Research*, 7(12), 4933.
- [98] Renukadevi, J., Sneha, P., Mridula, D. S., Nimithasree, K., & Sanjay, V. (2026). Bioengineered Isoflavone-Probiotic Functional Foods for Sustainable Modulation of Metabolic and Reproductive Health in PCOS. *Food Bioengineering*.
- [99] Rudic, J., Jakovljevic, V., Jovic, N., Nikolic, M., Sretenovic, J., Mitrovic, S., ... & Joksimovic Jovic, J. (2022). Antioxidative Effects of Standardized *Aronia melanocarpa* Extract on Reproductive and Metabolic Disturbances in a Rat Model of Polycystic Ovary Syndrome. *Antioxidants*, 11(6), 1099.
- [100] Sadrefozalayi, S., & Farokhi, F. (2014). Effect of the aqueous extract of *Foeniculum vulgare* (fennel) on the kidney in experimental PCOS female rats. *Avicenna Journal of Phytomedicine*, 4(2), 110.
- [101] Sakthivel V, Ilanthiraya S, Jeevanantham G, Aravindhan T, Priya K, Thirumurugan A, Larvicidal Activity Of Marine Macroalgae: A Comprehensive Review. *Int J Drug Deliv Technol*. 2026;16(4s): 908-917; DOI: 10.25258/ijddt.16.4s.106
- [102] Salmabadi, Z., Kouchesfahani, H. M., Parivar, K., & Karimzadeh, L. (2017). Effect of grape seed extract on lipid profile and expression of interleukin-6 in polycystic ovarian syndrome wistar rat model. *International Journal of Fertility & Sterility*, 11(3), 176.
- [103] Sandhiya T, Jeyabharathi S, Thirumurugan A. Exploration of Antimicrobial Drug Targets from Human Breast Milk *Lactobacillus* for the Control of Vaginal Infections. *Int J Drug Deliv Technol*. 2026;16(7s): 924- 933; DOI: 10.25258/ijddt.16.7s.98.
- [104] Sarma, S., Sockalingam, S., & Dash, S. (2021). Obesity as a multisystem disease: Trends in obesity rates and obesity-related complications. *Diabetes, Obesity and Metabolism*, 23, 3-16.
- [105] Shamsi, M., Nejati, V., Najafi, G., & Pour, S. K. (2020). Protective effects of licorice extract on ovarian morphology, oocyte maturation, and embryo development in PCOS-induced mice: An experimental study. *International Journal of Reproductive Biomedicine*, 18(10), 865.
- [106] Sherafatmanesh, S., Ekramzadeh, M., Tanideh, N., Golmakani, M. T., & Koolpeyma, F. (2020). The effects of thylakoid-rich spinach extract and aqueous extract of caraway (*Carum carvi* L.) in letrozole-induced polycystic ovarian syndrome rats. *BMC Complementary Medicine and Therapies*, 20, 1-13.
- [107] Shoaib, M., Saleem, A., Zeb, A., Khan, M. I., & Akhtar, M. F. (2023). Chemical characterization and ameliorating effect of *Centrathrum anthelminticum* extract against polycystic ovary syndrome in Wistar rats. *International Journal of Endocrinology*, 2023(1), 4978562. <https://doi.org/10.1155/2023/4978562>
- [108] Somarathna, R., Bednarz, T., & Mohammadi, G. (2022). Virtual reality for emotion elicitation—a review. *IEEE Transactions on Affective Computing*, 14(4), 2626-2645.
- [109] Soumya, V., Muzib, Y. I., Venkatesh, P., & Hariprasath, K. (2014). GC-MS analysis of *Cocus nucifera* flower extract and its effects on heterogeneous symptoms of polycystic ovarian disease in female Wistar rats. *Chinese Journal of Natural Medicines*, 12(9), 677-684. [https://doi.org/10.1016/S1875-5364\(14\)60103-5](https://doi.org/10.1016/S1875-5364(14)60103-5)
- [110] Stener-Victorin, E., Teede, H., Norman, R. J., Legro, R., Goodarzi, M. O., Dokras, A., & Piltonen, T. T. (2024). Polycystic ovary syndrome. *Nature Reviews Disease Primers*, 10(1), 27.
- [111] Stokes, A. H., Franklin, K., Fisher, D. E., Posobiec, L. M., Binazon, O., Tripathi, N., ... & Baumeister, J. (2021). Repeated dose toxicity study and developmental and reproductive toxicology studies of a respiratory syncytial virus candidate vaccine in rabbits and rats. *International Journal of Toxicology*, 40(2), 125-142.
- [112] Sudhakaran, G., Sreekutty, A. R., Choi, K. C., Valan Arasu, M., Guru, A., Karthick Raja Namasivayam, S., & Arockiaraj, J. (2026). Microbial Dysbiosis and Pathogenic Interplay in the Gut-Vaginal Axis: Implications for Polycystic Ovary Syndrome: A Critical Review. *Current Microbiology*, 83(4), 194.
- [113] Suriyakalaa, U., Ramachandran, R., Doulathunnisa, J. A., Aseervatham, S. B., Sankarganesh, D., Kamalakkannan, S., & Achiraman, S. (2021). Upregulation of Cyp19a1 and PPAR- γ in ovarian steroidogenic pathway by *Ficus religiosa*: A potential cure for polycystic ovary syndrome. *Journal of Ethnopharmacology*, 267, 113540. <https://doi.org/10.1016/j.jep.2020.113540>
- [114] Tahmasebi, F., Movahedin, M., & Mazaheri, Z. (2018). Antioxidant effects of calligonum extract on ovarian tissue of PCO model: An experimental study. *International Journal of Reproductive Biomedicine*, 16(10), 641.

- [115] Tahvilian, R., Gravandi, M. M., Noori, T., Papzan, A., Jamshidi, N., Iranpanah, A., & Shirooie, S. (2022). The therapeutic effect of methanolic extract *Bryonia dioica* Jacq. in a female rat model of polycystic ovary syndrome. *Journal of Reports in Pharmaceutical Sciences*, 11(1), 79-84.
- [116] Talukdar, R., Ajayan, R., Gupta, S., Biswas, S., Parveen, M., Sadhukhan, D., ... & Parameswaran, S. (2025). Chronic Kidney Disease Prevalence in India: A Systematic Review and Meta-Analysis From Community-Based Representative Evidence Between 2011 to 2023. *Nephrology*, 30(1), e14420.
- [117] Tay, C. T., Joham, A. E., & Teede, H. J. (2025). Key standards and principles for developing evidence-based clinical guidelines: balancing health professional, patient, funder, and government needs. *Fertility and sterility*.
- [118] Tovar, R., De Ceglia, M., Ubaldi, M., Rodríguez-Pozo, M., Soverchia, L., Cifani, C., ... & Decara, J. (2023). Administration of linoleoylethanolamide reduced weight gain, dyslipidemia, and inflammation associated with high-fat-diet-induced obesity. *Nutrients*, 15(20), 4448.
- [119] Unfer, V., Lepore, E., Forte, G., Hernández Marín, I., Wdowiak, A., & Pkhaladze, L. (2025). Hyperandrogenism in polycystic ovary syndrome and adrenal hyperplasia: finding differences to make a specific diagnosis. *Archives of Gynecology and Obstetrics*, 311(1), 25-32.
- [120] Wang, W., Barkat, M. Q., Amin, S., Alshammari, A., Albekairi, N. A., Manzoor, H., & Chen, Q. (2024). Pharmacological Appraisal of Aqueous Ethanolic Extract of *Cuminum cyminum* (Cumin Seeds) in Obesity and Endocrinopathies Associated with Polycystic Ovarian Syndrome in Animal Models. *Journal of Food Biochemistry*, 2024(1), 1184854.
- [121] Wydra, J., Wydra, A., Kucharczyk, P., Kapuściński, G., Zgliczyński, W., & Rabijewski, M. (2025). Selective estrogen receptor modulators and aromatase inhibitors in the treatment of functional male hypogonadism. *Endokrynologia Polska*.
- [122] Younas, A., Hussain, L., Shabbir, A., Asif, M., Hussain, M., & Manzoor, F. (2022). Effects of *Fagonia indica* on letrozole-induced polycystic ovarian syndrome (PCOS) in young adult female rats. *Evidence-Based Complementary and Alternative Medicine*, 2022(1), 1397060.
- [123] Zare, S., Nabiuni, M., Tayanloo, A., Hoseini, S., & Karimzadeh-Bardei, L. (2015). The effects of *Urtica dioica* extract on lipid profile, insulin resistance index and liver histology in polycystic ovary syndrome-induced Wistar rats. *Future Natural Products*, 1(2), 23-33.
- [124] Zhang, Y., & Xu, L. (2022). Comparative study of DHEA and letrozole induced polycystic ovary syndrome in post-pubertal rats. *Gynecological Endocrinology*, 38(5), 425-431.
- [125] Zheng, Y. H., Xu, Y., Ma, H. X., Liang, C. J., & Yang, T. (2021). Effect of High-Fat Diet on the Intestinal Flora in Letrozole-Induced Polycystic Ovary Syndrome Rats. *Evidence-Based Complementary and Alternative Medicine*, 2021(1), 6674965.
- [126] Zhou, J., Barry, J. A., Pan, J. X., Wang, F. F., Fu, Z. Z., Hardiman, P. J., & Qu, F. (2016). An *Atractylodes macrocephala* koidz extract alleviates hyperandrogenism of polycystic ovarian syndrome. *International Journal of Clinical and Experimental Medicine*, 9(2), 2758-2767